A Guide to Emulation, Implausibility and History Matching, and an Introduction to Designing Future Experiments.

Tuesday Session 2

UNICAMP Workshop on Bayesian Uncertainty Analysis of Complex Models

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Quick Overview of Tuesday

Bayesian uncertainty analysis of complex models
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- Session 1: a case study in Galaxy formation including
  - Emulation (proxy modelling)
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  - Introduction to **Designing future experiments**: what data should I pay for?
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  - Simple 1D emulator construction
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Guide to Emulation

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- Many calculations that take account of uncertainty need huge numbers of model evaluations.
- We have seen History Matching, but forecasting, making decisions to optimise certain outputs, designing new experiments etc. require even more model evaluations.
- Emulators, which represent our beliefs about the computer model, are very fast.
- Hence Emulators are essential for any serious analysis.
- We will now build a simple emulator.
For each output $f_i(x)$ we pick active variables $x^A$ then emulate using:

$$f_i(x) = \sum_j \beta_{ij} g_{ij}(x^A) + u_i(x^A) + \delta_i(x)$$
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- The $u_i(x^A)$ have covariance structure given by:

$$\text{Cov}(u_i(x_1^A), u_i(x_2^A)) = \sigma_i^2 \exp[-|x_1^A - x_2^A|^2/\theta_i^2]$$
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- The Emulators give the expectation \( E[f_i(x)] \) and variance \( \text{Var}(f_i(x)) \) at point \( x \) for each output given by \( i = 1, \ldots, 11 \), and are fast to evaluate.
Simple Emulator Equation

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- The first term is a regression term, often composed of low order polynomials in $x$ (or other appropriate deterministic functions), so
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  \]
- To really simplify things, let's set this polynomial to a constant \( \beta_0 \) (we will return to the polynomial later). Therefore we have:
  \[
  f(x) = \beta_0 + u(x)
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As we are going to use Bayes Linear methods to build our emulator, we need to specify a priori the \( \mathbb{E}(\beta_0), \text{Var}(\beta_0), \mathbb{E}(u(x)) \) and the covariance structure of \( u(x) \) which simply means the \( \text{Cov}(u(x), u(x')) \).
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- We then choose an appropriate covariance structure depending what we suspect the behaviour of the computer model \( f(x) \) to be: if it is pretty smooth as a function of \( x \) we may choose the Gaussian form:

  \[
  \text{Cov}(u(x), u(x')) = \sigma^2 \exp[-|x - x'|^2 / \theta^2]
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  where \( \sigma^2 \) and \( \theta \) are parameters we should specify.
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- In this case we specify \( E(\beta_0) \) corresponding to our beliefs about the mean of \( f(x) \), with \( \text{Var}(\beta_0) \) representing how unsure we are.
Simple 1-dimensional Sine Example

- Remember that $f(x)$ could represent any output of a complex model, so for a reservoir model, it could be the BHP or oil production at 1000 days, while $x$ would be a vector of inputs e.g. porosities, permeabilities, fault multipliers.
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- However, we will stick to a simple 1-dimensional example where

$$f(x) = \sin \left( \frac{2\pi x}{50} \right)$$
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- We imagine that due to computer time constraints we can only evaluate \( f(x) \) at 6 points and choose the (not ideal) locations:

\[x^{(j)} = 0, 10, 20, 30, 43, 50\]
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- We evaluate \( f(x^{(j)}) \) for \( j = 1 \) to 6, and gather the results into vector \( D \):

\[
D = (f(x^{(1)}), f(x^{(2)}), \ldots, f(x^{(6)}))^T
\]

\[
= \begin{pmatrix}
\sin\left(\frac{2\pi \times 0}{50}\right), \\
\sin\left(\frac{2\pi \times 10}{50}\right), \\
\ldots, \\
\sin\left(\frac{2\pi \times 50}{50}\right)
\end{pmatrix}^T
\]
Emulation: a 1D Example
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- We choose the parameters in the covariance function for $u(x)$ to be $\sigma = 1$ and $\theta = 15$ representing curves of moderate smoothness (over the range of $x$ values $[0, 50]$).
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- We now have all we need to use the Bayes Linear equations to update our prior beliefs $E(f(x))$ and $\text{Var}(f(x))$ about the behaviour of $f(x)$ given new run data $D$, to obtain adjusted beliefs $E_D(f(x))$ and $\text{Var}_D(f(x))$:

\[
E_D(f(x)) = E(f(x)) + \text{Cov}(f(x), D)\text{Var}(D)^{-1}(D - E(D))
\]

\[
\text{Var}_D(f(x)) = \text{Var}(f(x)) - \text{Cov}(f(x), D)\text{Var}(D)^{-1}\text{Cov}(D, f(x))
\]
Simple 1-dimensional Sine Example

- Everything on the right hand side of the BL update equations has been specified: as $f(x) = \beta_0 + u(x)$, $\beta_0 = 0$, $\sigma = 1$ and $\theta = 15$, we have:

  $$E(f(x)) = \beta_0, \quad \text{Var}(f(x)) = \sigma^2$$

  $$E(D) = (\beta_0, \ldots, \beta_0)^T$$
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\end{align*}
\]

- \( \text{Cov}(f(x), D) \) is a row vector of length \( n = 6 \) with \( j \)th component

\[
\text{Cov}(f(x), D)_j = \text{Cov}(f(x), f(x^{(j)}))
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- Similarly \( \text{Var}(D) \) is an \( n \times n \) matrix with \( (j, k) \) element

\[
\text{Var}(D)_{jk} = \text{Cov}(f(x^{(j)}), f(x^{(k)})) = \sigma^2 \exp \left\{ -\frac{\|x^{(j)} - x^{(k)}\|^2}{\theta^2} \right\}
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- Note that we can do the BL update for $f(x)$ for a single new untried input $x$, or we can simultaneously update for a set of $m$ new inputs, where $x$ would now become a vector of length $m$. 
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- Note that we can do the BL update for $f(x)$ for a single new untried input $x$, or we can simultaneously update for a set of $m$ new inputs, where $x$ would now become a vector of length $m$.

- Now $f(x)$ is a column vector of length $m$. 
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- In this case we use the same BL equations, but use $\text{Cov}(f(x), D)$ which is now an $m \times n$ matrix, $\text{Var}(f(x))$ is an $m \times m$ matrix, and $\text{E}(f(x))$ is a column vector of length $m$. 
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- You will try R code this afternoon that does this example with $n = 6$ and $m = 100$. 
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- Our emulator is complete and is represented as the adjusted expectation and variance of $f(x)$: $E_D(f(x))$ and $\text{Var}_D(f(x))$. 
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- We can now plot $\mathbb{E}_D(f(x))$ as a function of $x$ (in blue), and plot credible intervals (in red) as $\mathbb{E}_D(f(x)) \pm 3\sqrt{\text{Var}_D(f(x))}$.
Emulation: a 1D Example
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![Emulator of Model Output f(x)](image-url)
Emulation: a 1D Example

![Emulator of Model Output f(x)](chart)

- Note the way that $E_D(f(x))$ (the blue line) agrees precisely with the 6 known runs (the black dots) given by $D$. 
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- Note also that the credible interval (the red lines) shrinks to zero at the 6 known runs: this is due to $\text{Var}_D(f(x))$ going to zero at the points in $D$. 
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- Note also that the credible interval (the red lines) shrinks to zero at the 6 known runs: this is due to $\text{Var}_D(f(x))$ going to zero at the points in $D$.
- Today you will work with R code that does the above, and you will be able to play with $\beta_0, \sigma, \theta, D, x^{(j)}$ and the function $f(x)$. 
Simple 1-dimensional Sine Example: Implausibility

- Often we would want to emulate an expensive function because we are interested in history matching: finding the inputs $x$ that give acceptable matches between the outputs $f(x)$ and some history data $z$. 
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- $z$ is measured with observation error $e$, with variance $\sigma^2_e$, so were the model perfect, we would use an implausibility measure $I(x)$:

$$I^2(x) = \frac{|E_D(f(x)) - z|^2}{(\text{Var}_D(f(x)) + \text{Var}(e))}$$
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- Remember that high values of $I(x)$ imply that $x$ is unlikely to give a good match ($x$ is implausible), but low values just mean we are unsure about $x$. 
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- $z$ is measured with observation error $e$, with variance $\sigma_e^2$, so were the model perfect, we would use an implausibility measure $I(x)$:

$$I^2(x) = \frac{|E_D(f(x)) - z|^2}{(\text{Var}_D(f(x)) + \text{Var}(e))}$$

- Remember that high values of $I(x)$ imply that $x$ is unlikely to give a good match ($x$ is implausible), but low values just mean we are unsure about $x$.

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- For our example we take $z = -0.8$ and $\sigma_e^2 + \sigma_\epsilon^2 = 0.02^2$ and plot $I(x)$. 
Simple 1-dimensional Sine Example: Implausibility

Emulator of Model Output $f(x)$

Model Output $f(x)$

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Simple Example: 2nd Wave History Match

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- (This is a slight simplification, often we may create a new emulator from the \( x_{\text{wave2}}^{(j)} \) points alone, perhaps using the wave 1 emulator as prior).
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Emulator of Model Output $f(x)$

Implausibility vs. Impracticality
Simple Example: 2nd Wave History Match

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Implausibility $= f(x)$
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Input Parameter $x$

Model Output $f(x)$
Simple Example: 2nd Wave History Match

Emulator of Model Output \( f(x) \)

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Iterative History Matching for Reducing Input Space.

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7. If 6(a) true, generate a large number of acceptable runs from the final non-implausible volume $X$
More Advanced Emulators

- The simple emulator above had $f(x) = \beta_0 + u(x)$: this is a useful emulator but will fail for many functions that have high input dimension.
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- We can in principle specify prior expectations, variances and covariances for all the \( \beta_j \) terms: \( \mathbb{E}(\beta_j) \) and \( \text{Cov}(\beta_j, \beta_k) \), if we have informed beliefs about them.
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- We can obtain all the OLS estimates we need from the R function “lm()” (see later this afternoon).
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- $\delta(x)$ an uncorrelated nugget that has $E(\delta(x)) = 0$ and $Var(\delta(x)) = \sigma_\delta^2$. 
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- The identification of active inputs is also vital to the whole emulation process: it can greatly simplify a very complex and high dimensional function.
• If the polynomial or regression terms are good enough, we can build fast and useful emulators that are just linear models, with uncorrelated $u(x)$.
More Advanced Emulators: Conclusion

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- For an explicit demonstration of this, see our Galaxy papers.
We will now have a brief introduction to Designing future experiments or: what data should I pay for?

Often we want to use a complex model to predict the future, with appropriate uncertainty.

We would then want to use such predictions to inform us about decision we have to make.

For example, we may wish to choose the best experiment from a list of possible experiments, to achieve some scientific goal.

Similarly we may have the choice of paying for extra data, e.g. 4D seismic data, and wondered whether it is worth it.

We do this by History Matching first, then employing Decision Theory.

In the examples I show, we are going to judge future experiments based on how good we think they will be at reducing the size of the input space in a future history match: therefore our Utility will be linked to space reduction.
• Say we are interested in the concentration of a chemical which evolves in time. We will model this concentration as $f(x, t)$ where $x$ is a rate parameter and $t$ is time.
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- Note that normally we would **not** have the analytic solution for $f(x, t)$. 
• One “model run” with the input parameter $x = 0.4$
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• If we did not know the analytic solution for $f(x, t)$ this would be generated by numerically solving the differential equation.
Five model runs with the input parameter varying from $x = 0.1$ to $x = 0.5$
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The measurement is not a point but comes with measurement error.
• **Major question**: which values of $x$ ensure the output $f(x, t = 3.5)$ is consistent with the observations?
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• It would seem that $x$ has to be at least between 0.3 and 0.4.
To answer this, we can now discard other values of \( f(x, t) \) and think of \( f(x, t = 3.5) \) as a function of \( x \) only.
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That is take \( f(x) \equiv f(x, t = 3.5) \)
We can now plot the concentration $f(x,t)$ as a function of the input parameter $x$. 
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• Black horizontal line: the observed measurement of $f$
We can now plot the concentration $f(x)$ as a function of the input parameter $x$.

- Black horizontal line: the observed measurement of $f$
- Dashed horizontal lines: the measurement errors
If we know the analytical expression for \( f(x) = \exp(3.5x) \), then we can identify the values of \( x \) of interest.
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Ignoring the measurement error would lead to a single value for \( x \) but this is incorrect: we have to include the errors.
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Ignoring the measurement error would lead to a single value for \( x \) but this is incorrect: we have to include the errors.
• Uncertainty in the measurement of $f(x, t = 3.5)$ leads to uncertainty in the inferred values of $x$. 
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Hence we see a range (green/yellow) of possible values of \( x \) consistent with the measurements, with all the **implausible** values of \( x \) in red.
Another important form of uncertainty is that of model discrepancy related to how accurate we believe the model to be.
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This uncertainty arises from many issues e.g. is the form of the model (the differential equation) appropriate, is the model a simplified description of a more complex system, is there uncertainty in the initial conditions etc?
• Model discrepancy is represented as uncertainty around the model output $f(x)$ itself: here the purple dashed lines.
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• This results in more uncertainty in \( x \), and hence a larger range of \( x \) values.
Consider the graph of $f(x,t)$: in general we do not have the analytic solution of $f(x)$, here given by the dashed line.
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Instead we only have a finite number of runs of the model, in this case five.
The emulator can be used to represent our beliefs about the behaviour of the model at untested values of $x$, and is fast to evaluate.
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It gives both the expected value of $f(x)$ (the blue line) along with a credible interval for $f(x)$ (the red lines) representing the uncertainty about the model's behaviour.
Comparing the emulator to the observed measurement we again identify the set of $x$ values currently consistent with this data (the observed errors here have been reduced for clarity).
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Designing a Future Experiment.

- We have seen how we can use an emulator to learn about the input parameter $x$ even for a slow model.
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- We had measured the system at $t = 3.5$ and subsequently learnt about $x$. Now imagine we have to choose between two future experiments:
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  **Experiment A:** Measure $f(x, t)$ at $t = 2$ with same observed error as before.

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- We can use the model’s predictions at $t = 2$ and $t = 5$ to determine which experiment A or B is expected to be most informative about the input parameter $x$, given our knowledge about $f(x, t)$ at $t = 3.5$. 
Using the emulator we can choose several values of $x$ consistent with the measurement of $f(x, t)$ at $t = 3.5$, and perform corresponding runs of the model.
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- We can check the predictions made by these runs for $f(x, t = 2)$. 
- Using the emulator we can choose several values of $x$ consistent with the measurement of $f(x, t)$ at $t = 3.5$, and perform corresponding runs of the model.
- We can check the predictions made by these runs for $f(x, t = 2)$. 
• The predictions imply that any measurement of $f(x, t = 2)$ is highly unlikely to be informative for $x$.

• This is due to the measurement errors swamping the signal from the model output $f(x, t = 2)$. 

$\text{Concentration of } f(x,t)$

$\text{Time (t)}$
The predictions for \( f(x, t = 5) \) show a different conclusion.
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• For each possible measurement of $f(x, t = 5)$ it is highly likely that we will be able to rule out several more values of $x$ as implausible.
For one possible measurement, we see that non-implausible values of $x$ would lie approximately between 0.344 and 0.354, ruling out approximately 70% of the possible values of $x$. 
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• This high expected space reduction in $x$ implies that Experiment B, measuring $f(x, t)$ at $t = 5$, is clearly the best choice.
Simple Example: Conclusions

- We have hence used the results of the first experiment, measurement of $f(x, t = 3.5)$ to make predictions of the two possible experiments A and B.
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- We have hence used the results of the first experiment, measurement of $f(x, t = 3.5)$ to make predictions of the two possible experiments A and B.

- We then choose **Experiment B**, measurement of $f(x, t = 5)$, as it is the most efficient experiment for learning about $x$, as it has the highest expected space reduction (reduction in the range) of $x$, for the given measurement errors.
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- Note that although this method requires trusting the model predictions, in general we would incorporate a model discrepancy term to allow for a certain level of inaccuracy of the model.
• Small flowering plant related to cabbage and mustard.
Systems Biology: Arabidopsis

- **Small flowering plant** related to cabbage and mustard.
- One of the **model organisms** used for studying plant biology and the first plant to have its **entire genome sequenced**.
Systems Biology: Arabidopsis

- **Small flowering plant** related to cabbage and mustard.
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- Changes in it are easily observed, making it very useful.
Liu et. al. developed a kinetic model of hormonal crosstalk in Arabidopsis,
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- Here the input $x$ is a vector of length 32, but the output $f(x)$ is of length 96.
Arabidopsis Design of Experiment

• First major question: Is the model $f(x)$ currently consistent with the observed measurements $z$? If so can we identify the set $X(z)$ of all acceptable inputs?
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- **First major question**: Is the model $f(x)$ currently consistent with the observed measurements $z$? If so can we identify the set $X(z)$ of all acceptable inputs?

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- To answer this we need to:
  - Specify the class of possible experiments considered.
  - Use the results of the History Match to obtain model predictions for all future experiments that are consistent with current observations.
  - Choose the most efficient experiment based on an Expected Space Reduction criteria and complementary robustness considerations.

- This will result in a design for a new experiment that is expected to be highly informative about the input or rate parameters of the Arabidopsis system.
<table>
<thead>
<tr>
<th>Chemical Output</th>
<th>Initial concentration</th>
<th>Measurable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auxin</td>
<td>0.1</td>
<td>Yes</td>
</tr>
<tr>
<td>X</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>PLSp</td>
<td>0.1</td>
<td>Yes</td>
</tr>
<tr>
<td>Ra</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ra_star</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>0.1</td>
<td>Yes</td>
</tr>
<tr>
<td>ET</td>
<td>0.1</td>
<td>Yes</td>
</tr>
<tr>
<td>PLSm</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Re</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Re_star</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>CTR1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CTR1_star</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>IAA</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>cytokinin</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Reaction Network Model
### 32 Reaction Rates: 32 Input parameters

<table>
<thead>
<tr>
<th>Input</th>
<th>min</th>
<th>max</th>
<th>Input</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{1a}$</td>
<td>0.001</td>
<td>100</td>
</tr>
<tr>
<td>$k_2$</td>
<td>0.0002</td>
<td>20</td>
<td>$k_{2a}$</td>
<td>0.0028</td>
<td>280</td>
</tr>
<tr>
<td>$k_{2b}$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{2c}$</td>
<td>$1 \times 10^{-5}$</td>
<td>1</td>
</tr>
<tr>
<td>$k_3$</td>
<td>0.002</td>
<td>200</td>
<td>$k_{3a}$</td>
<td>0.00045</td>
<td>45</td>
</tr>
<tr>
<td>$k_4$</td>
<td>0.001</td>
<td>100</td>
<td>$k_5$</td>
<td>0.001</td>
<td>100</td>
</tr>
<tr>
<td>$k_6$</td>
<td>0.3</td>
<td>0.3</td>
<td>$k_{6a}$</td>
<td>0.0002</td>
<td>20</td>
</tr>
<tr>
<td>$k_7$</td>
<td>0.001</td>
<td>100</td>
<td>$k_8$</td>
<td>0.001</td>
<td>100</td>
</tr>
<tr>
<td>$k_9$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{10}$</td>
<td>$3 \times 10^{-7}$</td>
<td>0.03</td>
</tr>
<tr>
<td>$k_{10a}$</td>
<td>0.0005</td>
<td>50</td>
<td>$k_{11}$</td>
<td>0.005</td>
<td>500</td>
</tr>
<tr>
<td>$k_{12}$</td>
<td>0.0001</td>
<td>10</td>
<td>$k_{12a}$</td>
<td>0.0001</td>
<td>10</td>
</tr>
<tr>
<td>$k_{13}$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{14}$</td>
<td>0.003</td>
<td>300</td>
</tr>
<tr>
<td>$k_{15}$</td>
<td>$8.5 \times 10^{-5}$</td>
<td>8.5</td>
<td>$k_{16}$</td>
<td>0.0003</td>
<td>30</td>
</tr>
<tr>
<td>$k_{16a}$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{17}$</td>
<td>0.0001</td>
<td>10</td>
</tr>
<tr>
<td>$k_{18}$</td>
<td>0.0001</td>
<td>10</td>
<td>$k_{18a}$</td>
<td>0.001</td>
<td>100</td>
</tr>
<tr>
<td>$k_{19}$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{1vauxin}$</td>
<td>0.001</td>
<td>100</td>
</tr>
<tr>
<td>$k_{1vCK}$</td>
<td>0.001</td>
<td>100</td>
<td>$k_{1veth}$</td>
<td>0.001</td>
<td>100</td>
</tr>
</tbody>
</table>

- So now the input $x = (k_1, k_{1a}, k_2, k_{2a}, \ldots, k_{19}, k_{1vauxin}, k_{1vCK}, k_{1veth})$
Arabidopsis Model

\[
\frac{d\text{Auxin}}{dt} = \frac{k_{1a}}{1 + \frac{X}{k_1}} + k_2 + \frac{k_{2a} \text{ET}}{1 + \frac{\text{CK}}{k_{2b}}} \frac{\text{PLSp}}{k_{2c} + \text{PLSp}} - (k_3 + k_{3a}X)\text{Auxin} + k_{1vauxin} \text{IAA}
\]

\[
\frac{dX}{dt} = k_{16} - k_{16a} \text{CTR1}_{\text{star}} - k_{17}X
\]

\[
\frac{d\text{PLSp}}{dt} = k_8 \text{PLSm} - k_9 \text{PLSp}
\]

\[
\frac{d\text{Ra}}{dt} = -k_4 \text{AuxinRa} + k_5 \text{Ra}_{\text{star}}
\]

\[
\frac{d\text{Ra}_{\text{star}}}{dt} = k_4 \text{AuxinRa} - k_5 \text{Ra}_{\text{star}}
\]

\[
\frac{d\text{CK}}{dt} = \frac{k_{18a}}{1 + \frac{\text{Auxin}}{k_{18}}} - k_{19} \text{CK} + k_{1v} \text{CK}_{\text{cytokinin}}
\]

\[
\frac{d\text{ET}}{dt} = k_{12} + k_{12a} \text{AuxinCK} - k_{13} \text{ET} + k_{1v} \text{ET}_{\text{ACC}}
\]

\[
\frac{d\text{PLSm}}{dt} = \frac{k_6 \text{Ra}_{\text{star}}}{1 + \frac{\text{ET}}{k_{6a}}} - k_7 \text{PLSm}
\]

\[
\frac{d\text{Re}}{dt} = k_{11} \text{Re}_{\text{star}} \text{ET} - (k_{10} + k_{10a} \text{PLSp}) \text{Re}
\]

\[
\frac{d\text{Re}_{\text{star}}}{dt} = -k_{11} \text{Re}_{\text{star}} \text{ET} + (k_{10} + k_{10a} \text{PLSp}) \text{Re}
\]

\[
\frac{d\text{CTR1}}{dt} = -k_{14} \text{Re}_{\text{star}} \text{CTR1} + k_{15} \text{CTR1}_{\text{star}}
\]

\[
\frac{d\text{CTR1}_{\text{star}}}{dt} = k_{14} \text{Re}_{\text{star}} \text{CTR1} - k_{15} \text{CTR1}_{\text{star}}
\]

\[
\frac{d\text{IAA}}{dt} = 0, \quad \frac{dcytokinin}{dt} = 0, \quad \frac{d\text{ACC}}{dt} = 0
\]
Measurements of root hormone level.
Fundamental scientific questions:
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   (b) Can we identify the set \( \mathcal{X}'(z) \) of all such input or rate parameters?
Fundamental Scientific Questions

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1. (a) Are there any choices of rate parameters consistent with the 16 observed trends $z$?
   
   (b) Can we identify the set $\mathcal{X}(z)$ of all such input or rate parameters?

3. What design of future experiment will reduce this set $\mathcal{X}(z)$, and hence resolve uncertainty about the rate parameters?
Observed Trends plus 2000 runs of the model
Consider the graph of $f(x,t)$: in general we do not have the analytic solution of $f(x)$, here given by the dashed line.

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Implausibility Measures: Arabidopsis Model
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Iterative Input Space Reduction: 1D example

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We perform a 2nd iteration or wave of runs to improve emulator accuracy. The runs are located only at non-implausible (green/yellow) points. Now the emulator is more accurate than the observations, and we can identify the set of all $x$ values of interest.
Iterative Input Space Reduction: Arabidopsis Model Wave 2
Iterative Input Space Reduction: Arabidopsis Model Wave 3
Iterative Strategy for Arabidopsis Model: Wave 1
Iterative Strategy for Arabidopsis Model: Waves 1 and 2
Iterative Strategy for Arabidopsis Model: Wave 1, 2 and 3
Iterative Strategy for Arabidopsis Model: Wave 1, 2 and 3
Iterative Strategy for Arabidopsis Model: Waves 1 and 2

![Graph showing log increase in chemical from wild type with error bars for various conditions.](image-url)
Iterative Strategy for Arabidopsis Model: Waves 1, 2 and 3
Designing New Experiments

- We now have found several runs that belong to the set $\mathcal{X}$, consistent with 16 observed trends.
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- We are considering a class of 96 experiments formed from a combination of plant type, chemical measured and feeding regime, which leaves $96 - 16 = 80$ possible future experiments to choose from.
Designing New Experiments

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We hence expect to learn most efficiently about the rate parameters $x$ from this design of 4 experiments.
Designing new experiment: 1D example

- Using the emulator we can choose several values of $x$ consistent with the measurement of $f(x, t)$ at $t = 3.5$, and perform corresponding runs of the model.
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Designing new experiment: 1D example

The predictions imply that any measurement of $Y(t = 2)$ is highly unlikely to be informative for $x$.

This is due to the measurement errors swamping the signal from the model output $Y(t = 2)$. 
The predictions for \( Y(t = 5) \) show a different conclusion.
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For each possible measurement of $Y(t = 5)$ it is highly likely that we will be able to rule out several more values of $x$ as implausible.
For one possible measurement, see that non-implausible values of $x$ would lie between 0.344 and 0.354, ruling out 70% of the possible values of $x$. 
Designing new experiment: 1D example

- For one possible measurement, see that non-implausible values of $x$ would lie between 0.344 and 0.354, ruling out 70% of the possible values of $x$.
- This high expected space reduction in $x$ implies that Experiment B, measuring $f(x, t)$ at $t = 5$, is clearly the best choice.
History Matching Plots Plus New Outputs
Predictions for New Outputs
Space Cut Out Criteria for New Outputs
Space Cut Out Criteria for New Outputs

Choosing output 2
Space Cut Out Criteria for New Outputs

Choosing output 5

Expected Space Cut Out E[SI]
Predictions for New Outputs
• Consider the implausibility measure for a future measurement $z_i$:

$$I_{(i)}^2(x) = \frac{|E(f_i(x)) - z_i|^2}{\text{Var}(f_i(x)) + \text{Var}(\epsilon_i) + \text{Var}(e_i)}$$
Space Cut Out Criteria

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- We will cut out $x$ from further analysis if $I_{(i)}(x) > c_M$ as before, but now $z_i$ is a random quantity.
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• Given $z_i$, define the indicator function $I_i(x, z_i)$ s.t.

$$I_i(x, z_i) = \begin{cases} 
1 & \text{if } I_{(i)}(x) > c_M, \ x \text{ cut out} \\
0 & \text{if } I_{(i)}(x) < c_M, \ x \text{ not cut out}
\end{cases}$$ (1)
space cut out criteria

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- For given $z_i$, the fraction of space cutout $S_i$ due to output $i$ is:

$$S_i(z_i) = \frac{1}{V_{\mathcal{X}}} \int_{x \in \mathcal{X}} I_i(x, z_i) dx$$
Space Cut Out Criteria

- Given the best input $x^*$, and distributional assumptions for $z_i$ we have that:

  $$z_i|x^* \sim N(\mu_i(x^*), \sigma_i^2(x^*) + \text{Var}(\epsilon_i) + \text{Var}(e_i))$$

  with $\mu_i(x^*) = \mathbb{E}_D(f_i(x = x^*))$ and $\sigma_i(x^*) = \text{Var}_D(f_i(x = x^*))$. 
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- Therefore the expected space cut out $S_i$ given $x^*$ is then

  $$
  \mathbb{E}(S_i|x^*) = \frac{1}{V_X} \int \int_{z_i} \int_{x \in X} I_i(x, z_i) \pi(z_i|x^*) dx dz_i
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• and the expected space cut out $S_i$ for new output $i$ is

$$\mathbb{E}(S_i) = \frac{1}{V^2\mathcal{X}} \int_{x^* \in \mathcal{X}} \int_{z_i} \int_{x \in \mathcal{X}} I_i(x, z_i)\pi(z_i|x^*)dxdz_idx^*$$
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- and the expected space cut out $S_i$ for new output $i$ is

$$\mathbb{E}(S_i) = \frac{1}{V\chi^2} \int_{x^* \in \chi} \int_{z_i} \int_{x \in \chi} I_i(x, z_i)\pi(z_i|x^*)dx dz_i dx^*$$

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- In fact we want to choose 4 outputs $i, j, k, l$ such that the analogous expected space cut out $\mathbb{E}(S_{i,j,k,l})$ is maximised.
Approximate Space Cut Out Criteria

- Integrals are expensive so we use the set of $n_a$ acceptable runs $x_j$, $j = 1, \ldots, n_a$ where $x_j \in \mathcal{X}$ to approximate the integrals.
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• In which case $E(S_i)$ becomes

$$E(S_i) \approx \frac{1}{n_a n_{\text{sim}}} \sum_{k=1}^{n_a} \sum_{a=1}^{n_{\text{sim}}} \sum_{j=1}^{n_a} I_i(x_j, z^a_i)$$

• where we approximate the $z_i$ integral by simulating $n_{\text{sim}}$ draws of $z_i$ from $\pi(z_i|x^*_k)$ for each $x^*_k$. Can do analytically in some cases.
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- Again, we are interested in the analogous multivariate quantity \( \mathbb{E}(S_{i,j,k,l}) \).
Experimental Design Results: 4 new experiments chosen

- Selected outputs by stepping up to 8 outputs, then back down to 4: robust.
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- Sensitivity analysis: performed two calculations with high/low model discrepancy and observed errors: same choice of outputs in both cases.
Experimental Design Results: 4 new experiments chosen

- Selected outputs by **stepping up to 8 outputs, then back down to 4**: robust.

- **Sensitivity analysis**: performed two calculations with high/low model discrepancy and observed errors: **same choice of outputs** in both cases.

- The **four most informative experiments** chosen to maximise $E(S_{i,j,k,l})$:

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<th>chemical measured</th>
<th>feeding regime</th>
<th>expected space cut</th>
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- First two experiments completed.
Seven day old Columbia wildtype plants were transferred to media containing either cytokinin and auxin (BAP + IAA), an ethylene precursor and auxin (ACC + IAA) or no hormone treatment. After three hours, the relative abundance (expression) of the POLARIS mRNA was measured with qPCR. Three separate biological replicates were used and error bars represent the standard error of the mean.
Iterative Input Space Reduction: Arabidopsis Model Wave 2
Iterative Input Space Reduction: Arabidopsis Model Wave 3
Arabidopsis Model with 2 New Results
• Large reduction in input space due to just 2 new experiments.
Concluding Comments

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- All these calculations are designed to be efficient: approximations used are very beneficial.
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- We can also design experiments to challenge the model, i.e. to validate it if necessary.
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- The correct treatment of uncertainty is vital: without this, any analysis will be problematic and untrustworthy.

- The emulation methods we describe can be used to exhaustively explore model features (helpful when developing models).

- Due to the need to synthesis many sources of uncertainty within one coherent calculation, a Bayesian approach is ideal.
**References**

**History Matching on Galaxy simulation papers:**


**The Bayes Linear Book:**


**Arabidopsis Model:**

Developments in Emulation

- Much work in the emulation of deterministic models (much to be done too!). Some decent papers are (see Managing Uncertainty in Complex Models website http://www.mucm.ac.uk):
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**History Matching and use of fast approximate models:**


**Probabilistic Calibration:**


**Classic book on design:**

Developments in Emulation

A good introductory tutorial:

More advanced model discrepancy:
M. Goldstein and J.C.Rougier (2008). Reified Bayesian modelling and inference for physical systems (with discussion), JSPI.

Sensitivity Analysis:

Fast Multivariate Emulators:
Developments in Emulation

Example of dimension reduction on the outputs:
Higdon, D., Gattiker, J., Williams, B. and Rightley, M., Computer Model Calibration Using High-Dimensional Output, JASA (2008), Vol. 103, No. 482,

Dimension reduction on the outputs using Principal Variables:
Cumming, J., A. and Goldstein, M., Bayes linear uncertainty analysis for oil reservoirs based on multiscale computer experiments, (2009), Handbook of Bayesian Analysis, eds A O’Hagan and M West, Oxford University Press.

Dynamic Emulation:

Assessing internal model discrepancy by adding noise to model:
Developments in the Emulation of Stochastic Models

For Bayes Linear Stochastic Emulation:


Vernon, I., & Goldstein, M. Bayes Linear Emulation and History Matching of Stochastic Systems Biology Models, in preparation.

For Bayes Linear Variance Learning see:


For the Arabidopsis model used in this talk see (further papers in preparation):

Developments in the Emulation of Stochastic Models

Emulation in Epidemiology


M. Farah, P. Birrell, S. Conti, and D. De Angelis (2013), ”Bayesian Emulation and Calibration of a Dynamic Epidemic Model for H1N1 Influenza”. Submitted, under review.
Developments in the Emulation of Stochastic Models

More emulation of stochastic systems biology models:

Design for stochastic models (needs simple heteroscedasticity):